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Clinical Behavior of Borderline Ovarian Tumors: A Study of 150 Cases

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Background: We evaluated the clinical features, treatment, and survival status of the patients with borderline ovarian tumors.

Methods: A retrospective review of the charts of 150 patients with borderline ovarian tumor registered at the Tokai Ovarian Tumor Study Group from January 1, 1980, to December 31, 1994, was conducted to obtain clinical and pathological information.

Results: In stage II and III disease, the numbers of patients with no residual tumor, residual tumor of <2 cm, 2–5 cm, and >5 cm were 9, 10, 3, and 3, respectively. The sizes of residual tumors and corresponding clinical response to chemotherapy were as follows: residual tumor of <2 cm, complete response (CR), 6 patients; no change (NC), 2; progressive disease (PD), 2; tumors 2–5 cm, NC, 1 patient, PD, 2; tumors >5 cm, PD, 3 patients. The survival for patients with residual tumor <2 cm was significantly better than for those with residual tumor from 2–5 cm and of >5 cm ($P < 0.05$). The survival for patients with stage II and III serous tumor was significantly longer than that for patients with stage II and III mucinous tumor ($P < 0.05$).

Conclusion: In advanced borderline ovarian tumor, the prognosis of patients with gross residual tumor after initial surgery, and especially with mucinous tumor, was poor. J. Surg. Oncol. 64:147–152.

KEY WORDS: **borderline ovarian cancer; advanced stage; residual tumor; treatment**

INTRODUCTION

Epithelial ovarian tumors of borderline malignancy have been studied intensively over the past decade. The clinical entity was initially reported by Taylor in 1929 [1], in patients who were considered terminal because the ovarian tumors had extended beyond the ovaries with wide peritoneal implants at initial laparotomy, but who survived and were well for many years. He recorded the tumors histologically as ''hyperplastic papillary cystadenoma'' and then as ''semimalignant'' and ''borderline.'' The new concept of borderline tumor was accepted by the International Federation of Gynecology and Obstetrics (FIGO) in 1961. The classification was

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TABLE I. Presenting Symptoms of Borderline Ovarian Cancer

Symptom[a]	No. patients (%)			
	Serous	Mucinous	Endometrioid	Total
Asymptomatic found on routine examination	13 (23.2)	8 (8.9)	1 (25.0)	22 (14.7)
Abdominal pain	22 (39.3)	24 (26.7)	0 (0.0)	26 (17.3)
Increasing girth or abdominal distension	10 (17.9)	44 (48.9)	2 (50.0)	56 (37.3)
Abdominal lump	7 (12.5)	10 (11.1)	0 (0.0)	17 (11.3)
Change of bowel habit	2 (3.6)	8 (8.9)	0 (0.0)	10 (6.7)
Atypical genital bleeding				
premenopausal abnormal uterine bleeding	3 (5.4)	9 (10.0)	0 (0.0)	12 (8.0)
postmenopausal uterine bleeding	1 (1.8)	0 (0.0)	1 (25.0)	2 (1.3)
Dysuria	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.7)
Pollakisuria	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.7)

[a]Some patients presented with a combination of symptoms.

adopted in 1970 and became effective on January 1, 1971 [2]. The World Health Organization (WHO) subsequently adopted a similar classification of ovarian tumor in 1973 [3]. It is now realized that when borderline ovarian tumors are localized to one or both ovaries (FIGO, stage I), the prognosis is excellent [4–6] and no further adjuvant treatment is needed after initial operation. There is, however, considerable controversy over the most appropriate management of patients with extraovarian disease. Although some patients enjoy prolonged survival even if the tumor extends to extraovarian lesions, there have been reports of others whose tumors were progressive despite aggressive cytoreductive surgery and chemotherapy [7]. The purpose of this retrospective review as to evaluate the clinical features, treatment, and survival status of 150 patients with borderline ovarian tumors treated at the Tokai Ovarian Tumor Study Group.

MATERIALS AND METHODS

A retrospective review of the charts of 150 patients with borderline ovarian tumor registered at the Tokai Ovarian Tumor Study Group, which consisted of the Department of Obstetrics and Gynecology in Nagoya University School of Medicine and its related hospitals from January 1, 1980 to December 31, 1994, was conducted to obtain information regarding age, parity, menopausal status, presenting symptoms, observations at the time of laparotomy, and treatment. All ovarian tumors were classified by the same pathologist (N. Nakashima) in accordance with the WHO criteria for histological typing [3]. The stage was designated according to the FIGO system [8]. In the early part of the study, tumor staging was retrospective and based on a review of operation notes and pathology reports. In the latter part of the study, more attention was paid to accurate staging at initial laparotomy and to the detection of spread. Follow-up was achieved by reviewing the records of the hospital, private consultants, or by contacting patients and reviewing them personally. Statistical comparison were made by the Mann-Whitney test to determine the significance of each nonparametric factor. Survival curves were calculated by the Kaplan-Meier method. The Log-Rank test was used for statistical analysis of survival rates.

RESULTS

The mean age of the patients in this study was 44.3 years (range 12–77 years), younger than those with invasive carcinoma [9]. The mean age of patients with serous tumors was 43.8 years (range 14–74 years), mucinous tumors 49.0 (range 43–54), and endometrioid tumors 49.0 (range 43–53). There was no difference in mean age among patients with different histologic types of tumors. Of the patients, 67% were premenopausal and 25% were nulligravid.

The presenting symptoms are summarized in Table I. The most common presenting symptoms of patients with serous tumors were abdominal pain (39.3%), increasing girth or abdominal distention (17.9%), and abdominal lump (12.5%), although 23.2% were asymptomatic with a mass being detected incidentally on routine examination. Patients with mucinous tumors complained more often of increasing girth or abdominal distension (48.9%) than those with serous tumors. Some patients experienced abdominal pain (26.7%), but the mucinous tumors were occasionally discovered on routine examination (8.9%).

The histological types and corresponding stages of these neoplasms were 56 serous (Stage IA: 29 patients; Stage IB: 2 patients; Stage IC: 9 patients; Stage IIB: 1 patient; Stage IIIC: 10 patients), 90 mucinous (Stage IA: 52 patients; Stage IB: 3 patients; Stage IC: 26 patients; Stage IIC: 1 patient; Stage IIIB: 1 patient; Stage IIIC: 7 patients), 4 endometrioid (Stage IA: 2 patients; Stage IC: 2 patients) (Table II). The incidence of patients with

TABLE II. Borderline Ovarian Cause: FIGO Stage and Histological Type

	Serous	Mucinous	Endometrioid	Total
Stage I				
A	29	52	2	83
B	2	3	0	5
C	9	26	2	37
Stage II				
A	0	0	0	0
B	1	0	0	1
C	5	1	0	6
Stage III				
A	0	0	0	0
B	0	1	0	1
C	10	7	0	17
Total	56	90	4	150

extraovarian implants was higher in those with serous tumor than with mucinous tumor.

The size of the primary borderline ovarian tumors ranged from 30 mm to 500 mm, with a mean size of 146 ± 74.4 mm. The mean diameter of mucinous tumors was 169 ± 77.4 mm, and those of serous and endometrioid tumors were 110 ± 54.5 mm and 120 ± 58.9 mm, respectively. Mucinous tumors were significantly larger than serous and endometrioid tumors ($P < 0.01$).

Sixty-four of the patients with stage I disease underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Fifty-eight patients were treated with conservative therapy, 48 with unilateral salpingo-oophorectomy with or without biopsy of the contralateral ovary, and 6 with unilateral salpingo-oophorectomy and hysterectomy. Four patients had ovarian cystectomy with or without biopsy of the contralateral ovary. Three patients were treated with bilateral salpingo-oophorectomy. In patients with stage I disease, 24.0% (30 of 125) underwent omentectomy and 12.8% (16 of 125) pelvic and/or paraaortic lymphadenectomy. Most of patients with stage I tumors received adjuvant chemotherapy by oral administration for one year after initial surgery.

Table III lists the treatment and subsequent status of the 25 patients (7 patients with stage II and 18 patients with stage III) who had extraovarian implants. Sixteen patients had serous tumors and nine patients had mucinous tumors. Most of the extraovarian disease spread in the abdominal cavity. Six patients had retroperitoneal nodal involvement and two of these patients had metastatic sites only in the pelvic lymph nodes. In this study, patients with advanced disease underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy or sampling, omentectomy, and cytoreductive surgery. The numbers of patients with no residual tumor, residual tumor of <2 cm, 2–5 cm, and >5 cm after initial surgery, by histological type were as follows: serous tumor 8, 6, 0, and 2, mucinous tumor 1, 4, 3, and 1. Eight (50%) of 16 patients with advanced serous tumor had no residual tumor, although only one (11%) of nine patients with advanced mucinous tumor had no residual tumor; 23 (92%) of those patients were treated with cisplatin-based chemotherapy. The sizes of residual tumors and corresponding clinical response to chemotherapy were as follows: residual tumor of <2 cm: complete response (CR), 6 patients, no change (NC), 2, progressive disease (PD), 2; tumor size 2–5 cm: NC, 1 patient, PD, 2; tumor size >5 cm: PD, 3 patients. One of nine patients with no residual tumor had a recurrence in the sigmoid colon 5 months after surgery. This patient with stage IIIc mucinous tumor at the initial surgery underwent partial resection of the sigmoid colon but died as a result of the disease 23 months after initial surgery. One of six patients with complete response had a recurrence in the lung 36 months after surgery and died as a result of disease despite adjuvant chemotherapy 72 months after initial surgery.

Follow-up of the 150 patients ranged from 2–140 months, with a mean of 61 months. Clinical life table analysis gave overall 5-and 10-year survival rates for all patients of 94.7% and 89.2%, respectively. The patients with serous and mucinous tumors had 5- and 10-year survival rates of 95.8% and 88.8%, and 93.6% and 89.5%, respectively. Patients with endometrioid tumors had 100% 5-year survival. The Log-Rank test indicated no difference in survival curves by histological types. Clinical life table analysis gave 5-year survival rates for patients with stage I, II, and III disease of 100, 50.0, and 64.5%, respectively. No patient with stage I disease had a recurrence, but two patients died of unrelated causes. The Log-Rank test indicated a difference in the survival curves by stage. Examination of three survival curves demonstrated that the survival curves for patients with stages II and III were significantly different from that for patients with stage I ($P < 0.001$) (Fig. 1). The patients with serous and mucinous tumors of stages II and III had 5- and 9-year survival rates of 91.7% and 73.3%, and 38.9% and 13.0%, respectively. The survival curve for patients with serous tumor of stages II and III was significantly different from that for patients with mucinous tumor of stage II and III ($P < 0.05$) (Fig. 2). Figure 3 shows the survival curves by residual tumor size. The survival curve for patients with residual tumor <2 cm was significantly different from those for patients with residual tumor from 2–5 cm and of >5 cm ($P < 0.05$). The survival curve for patients with no residual tumor and residual tumors of <2 cm was significantly different from that for patients with residual tumors from 2–5 cm and >5 cm ($P < 0.001$).

DISCUSSION

Borderline ovarian tumors account for 9.2% to 16.3% of ovarian malignancies [4,10,11], with the serous and

TABLE III. Patients with Borderline Ovarian Tumors and Extraovarian Tumor Implants: Clinical Features and Location of Implants

Age	Histology	Stage	Original implant site	Initial operation[a]	Residual tumor	Adjuvant chemo-therapy[b]	Clinical response[c]	Follow-up (mo)	Status[d]
50	Serous	IIb	pelvic peritoneum	TAH+BSO+LN+OM	(−)	BVP	-	43	NED
28	Serous	IIc	fallopian tube, pelvic peritoneum	TAH+BSO	<2 cm	MFCP	CR	122	NED
49	Serous	IIc	fallopian tube, pelvic peritoneum	TAH+BSO+LN+OM	(−)	BVP	-	36	NED
20	Serous	IIc	pelvic peritoneum	TAH+BSO	(−)	BVP	-	4	NED
47	Serous	IIc	fallopian tube, cul-de-sac	TAH+BSO+LN+OM	(−)	BVP	-	22	NED
14	Serous	IIc	fallopian tube, uterine serosa	RSO+LN+OM	(−)	BVP	-	10	NED
58	Mucinous	IIc	fallopian tube, uterine serosa	TAH+BSO	<2 cm	MFCP	PD	45	DOD
21	Mucinous	IIIb	cul-de-sac, omentum	LSO+OM	<2 cm	CAP	CR	72	DOD
58	Serous	IIc	pelvic peritoneum, colon serosa, momentum	exploratory ope	5 cm<	MFC	PD	62	DOD
65	Serous	IIIc	uterine serosa, fallopian tube, pelvic peritoneum, omentum	TAH+BSO+OM	<2 cm	CAP	CR	107	NED
42	Serous		fallopian tube, omentum, abdominal peritoneum	TAH+BSO+OM	<2 cm	CAP	CR	91	NED
62	Serous	IIIc	abdominal peritoneum, colon serosa, momentum, pelvic&para-aortic lymph node	TAH+BSO+LN+OM	<2 cm	BVP	CR	23	NED
35	Serous	IIIc	pelvic lymphnode	TAH+BSO+LN+OM	(−)	CAP	-	65	NED
52	Serous	IIIc	fallopian tube, abdominal peritoneum, colon serosa, omentum	exploratory ope	5 cm<	CAP	PD	13	DOD
38	Serous	IIIc	pelvic lumphnode	TAH+BSO+LN+OM	(−)	PP	-	15	NED
35	Serous	IIIc	fallopian tube, cul-de-sac, pelvic lymph node	TAH+BSO+LN+OM	(−)	PP	-	18	NED
34	Serous	IIIc	fallopian tube, rectum serosa, pelvic lymph node	TAH+BSO+LN+OM	<2 cm	BVP	NC	11	AWD
30	Serous	IIIc	abdominal peritoneum, bowel serosa, omentum, pelvic&para-aortic lymph node	TAH+BSO+LN+OM	<2 cm	PP	NC	4	AWD
60	Mucinous	IIIc	omentum, rectum serosa	BSO	<2 cm	MFC	PD	21	DOD
61	Mucinous	IIIc	omentum, abdominal peritoneum, bowel serosa	TAH+BSO+OM	<2 cm	MFCP	CR	110	NED
61	Mucinous	IIIc	omentum, abdominal peritoneum	RSO+OM	2–5cm	MFCP	PD	9	DOD
48	Mucinous	IIIc	pelvic peritoneum, ileum serosa, omentum	TAH+BSO+OM	(−)	CAP	-	23	DOD
51	Mucinous	IIIc	fallopian tube, abdominal peritoneum, uterine&bowel serosa, omentum	OM	5 cm<	CAP	PD	29	DOD
63	Mucinous	IIIc	fallopian tube, abdominal&pelvic peritoneum, bowel serosa, omentum	TAH+BSO+OM	2–5 cm	CAP	PD	10	DOD
77	Mucinous	IIIc	fallopian tube, abdominal peritoneum, uterine&bowel serosa, omentum	RSO+OM	2–5 cm	UFT	NC	21	AWD

[a]TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LN, lymphadenectomy; OM, omentectomy; RSO, right salpingo-oophorectomy; LSO, light salpingo-oophorectomy.
[b]BVP, bleomycin, vinblastin; cisplatin; PP, cisplatin; carboplatin; MFC, mitomycin C, 5-fluorouracil, Cytarabine; UFT, tegafur; MFCP, mitomycin C, 5-fluorouracil, cytarabine, cisplatin, CAP, cyclophosphamide, doxorubicin, cisplatin.
[c]CR, complete response; PD, progressive disease; PR, partial response; NC, no change.
[d]NED, no evidence of disease; DOD, dead of disease; AWD; alive with residual disease.

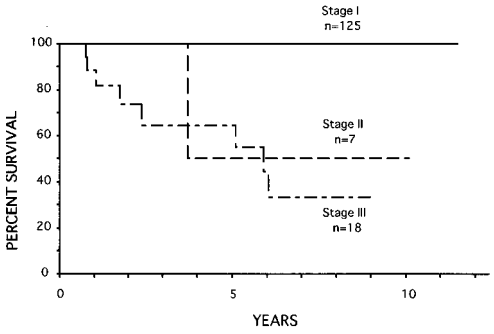

Fig. 1. Surviv1al of patients with borderline ovarian tumors according to clinical stage of tumor.

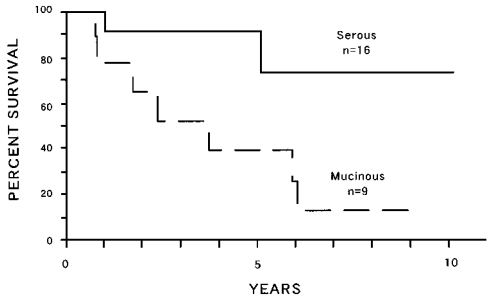

Fig. 2. Survival of patients with borderline ovarian tumors of stages II and III according to histological type.

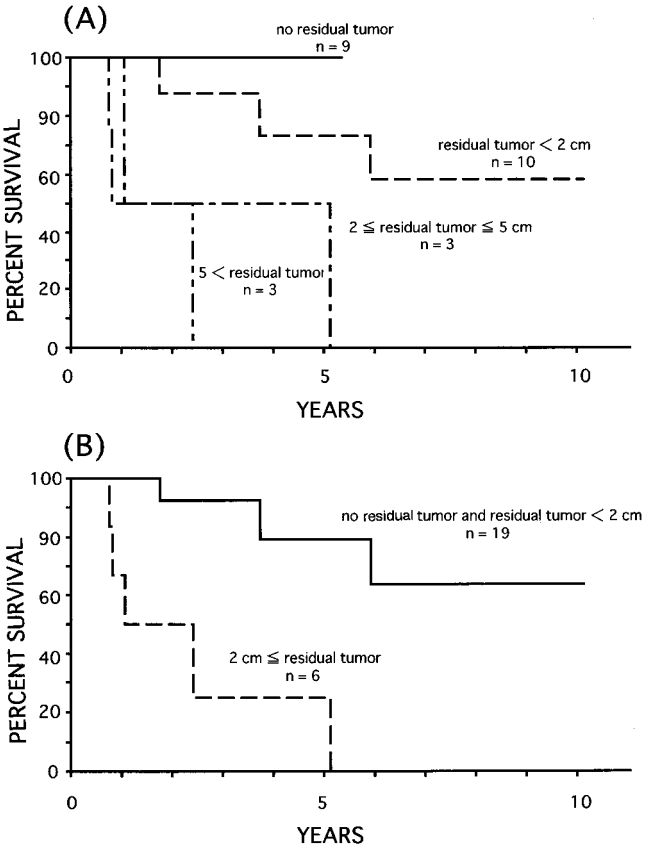

Fig. 3. Survival of patients with borderline ovarian tumors according to residual tumor size. **A.** Four categories (no residual, residual tumor <2 cm, 2 ≦residual tumor ≦5, 5 < residual tumor). **B.** Two categories (no residual and residual tumor <2 cm, 2 ≦residual tumor).

mucinous types making up the vast majority of cases. Kliman et al. [5] found 51.3% of 76 tumors to be mucinous and 38.2% serous, and in this study 60% of 150 tumors were mucinous and 37% serous.

It has been established in several reports that borderline tumor occurs in younger patients than in those who develop invasive carcinomas [4,12], and the mean age was 44.3 years in this study. Reproductive potential is therefore a concern to many patients with borderline tumor. Of tumors in this study, 83% were at stage I at diagnosis, which is similar to the report by Aure et al. [12]. Since there were no patients with stage I disease who died of tumors, we believe that young stage I patients who wish to preserve childbearing potential should be managed by unilateral salpingo-oophorectomy with careful follow-up providing an adequate surgical staging procedure has been performed. This is in agreement with the conclusions of other authors [4,6,13].

From 16–18% of borderline tumors are stage II or greater [13,14]. In this study, 17% of 150 borderline tumors were stage II or III, and extraovarian disease was observed more often with serous (29%) than mucinous tumors (10%), which is in agreement with the observations of other authors [10,15]. The spread of borderline tumor is usually transperitoneal, but occurs much less frequently than in the carcinomas. Retroperitoneal nodal spread occurs occasionally [4]. In this study, 27 patients underwent a pelvic or para-aortic lymphadenectomy at the initial surgery. Six of these patients had metastatic borderline ovarian tumor in the lymph nodes. Two of six patients had metastatic sites only in the pelvic lymph node.

The clinical stage of disease is of prime importance in determining the ultimate prognosis. It has been reported that the overall 5-year survival rate for patients with stage I disease was 95% [14,16–20], but that the survival rates in stage II and stage III fell to 40–75% and 56–65% [16–18], respectively. In our study the survival rates for patients with stages I, II, and III disease were 100, 50.0, 64.5%, respectively. Thus it is apparent that patients with stage I disease have an excellent prognosis, whereas a number of patients with more advanced disease will not survive. The patients with serous and mucinous tumors of stage II and III had 5- and 9-year survival rates of 91.7% and 73.3%, and 38.9% and 13.0%, respectively, although there was no difference in overall survival rate by histological types. The patients with advanced mucinous tumor have a poor prognosis, which shows the need to develop effective treatment for advanced mucinous tumor.

Postoperative treatment of borderline tumors is com-

plex and controversial. It has been reported that there was no difference in survival rate between patients treated with adjuvant therapy and those treated with surgery alone [4,6,13,14]. In our study most of patients received adjuvant chemotherapy. No patient with stage I disease had a recurrence, although it has been reported that 2–7% of patients with stage I borderline tumor showed a recurrence [6,21].

The effectiveness of adjuvant chemotherapy for patients with borderline tumors that have spread beyond the ovary (regardless of whether they have residual disease) is unclear. No study has yet demonstrated a survival advantage for treatment with adjuvant chemotherapy for patients with advanced borderline tumor. However, two retrospective studies have demonstrated a response to chemotherapy based upon findings at second-look laparotomy [22,23]. As in other reports, all of 25 patients (16 patients with and 9 patients without residual tumor) in this study received adjuvant chemotherapy. Five of the 16 patients with residual tumor had clinically complete response, and all of these five patients had residual tumors of <2 cm. The response rate of patients with residual tumors of <2 cm was 50% (5/10). This study confirmed the significance of residual tumors in patients with stage II and III of borderline malignancy. In our study the efficacy of adjuvant chemotherapy cannot be evaluated. Studies investigating the value of adjuvant chemotherapy in borderline ovarian tumor should consider including a no-treatment group.

CONCLUSION

In summary, patients with borderline ovarian tumors should undergo hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy or sampling, and omentectomy to provide adequate staging. For patients with advanced disease, cytoreductive surgery should be performed additionally. As a matter of course, conservative therapy is indicated for stage I patients who desire future fertility. In this study, all patients with advanced disease received adjuvant chemotherapy, but cisplatin-based chemotherapy had no effect in patients with gross residual tumor, especially with mucinous tumor. Our results indicate that in the clinical treatment of patients with borderline ovarian tumors, it is necessary to develop methods for identification of those tumors that are more likely to run a bad course, and effective therapies for the occasional patient who has recurrent or progressive disease.

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